Interactive CardioVascular and Thoracic Surgery

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Interact CardioVasc Thorac Surg 2010;10:37-42; originally published online Oct 8, 2009;
DOI: 10.1510/icvts.2009.214551

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doi:10.1510/icvts.2009.214551

INTERACTIVE CARDIOVASCULAR AND THORACIC SURGERY

Interactive CardioVascular and Thoracic Surgery 10 (2010) 37–42

www.icvts.org

Institutional report - Coronary

Transfusion of red blood cells: the impact on short-term and long-term survival after coronary artery bypass grafting, a ten-year follow-up

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Received 16 June 2009; received in revised form 12 August 2009; accepted 7 September 2009

Abstract

Transfusion of red blood cells (RBC) and other blood products in patients undergoing coronary artery bypass grafting (CABG) is associated with increased mortality and morbidity. We retrospectively analyzed data of patients who underwent an isolated coronary bypass graft operation between January 1998 and December 2007. Mean follow-up was 1696±1026 days, with exclusion of 122 patients lost to follow-up and 80 patients who received 10 units of RBC. Of the remaining patients, 8001 (76.7%) received no RBC, 1621 (15.2%) received 1–2 units of RBC, 593 (5.7%) received 3–5 units and 220 (2.1%) received 6–10 units. The number of transfused RBC was a predictor for early but not for late mortality. When compared to expected survival, survival of patients not receiving any blood product was better, while survival of patients receiving >3 units of RBC was worse. Transfusion of RBC is an independent, dose-dependent risk factor for early mortality after revascularization. Compared to expected survival, receiving no RBC improves patient long-term survival, whereas receiving three or more units of RBC significantly decreases patient survival.
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Keywords: Revascularization; Blood cells; Survival; Epidemiology; Coronary disease

1. Introduction

Transfusion of red blood cells (RBC) in patients undergoing coronary artery bypass grafting (CABG) is associated with increased mortality and morbidity [1–4]. Transfusion of RBC as a risk factor for early mortality has been well established whereas the effect of RBC transfusion on late mortality has been less well described.

This study analyzes the effect of perioperative transfusion of RBC on short- and long-term mortality after CABG in our centre and compares survival rates with expected survival based on the general Dutch population.

2. Methods

The study was performed after permission of the local Medical Ethics Committee. We studied the data of all patients undergoing isolated CABG in our center between January 1998 and December 2007. Clinical data were prospectively collected in our database. Patients were classified into four groups stratified by number of units of transfused RBC: group 1 did not receive any unit of RBC; $n=6828$ (65.5%), group 2 received 1–2 units; $n=2371$ (22.7%), group 3 received 3–5 units; $n=900$ (8.6%) and group 4 received 6–10 units; $n=326$ (3.1%). Patients with >10 units of transfused RBC were excluded from further analyses ($n=69$).

Normothermic extra-corporeal circulation (ECC) was performed using non-pulsatile flow. Cold crystalloid cardioplegia ('St Thomas' solution) or warm blood cardioplegia was used to induce and maintain cardioplegic arrest, according to the surgeon's preference. All patients undergoing CABG with the use of ECC, received a low dose aprotinin (2 million kallikrein inactivating units) during ECC.

Follow-up data concerning mortality of patients were gathered using databases of health insurance companies, general practitioners and local authorities. Early mortality was defined as any cause mortality ≤30 days postoperatively, while late mortality was defined as any cause mortality >30 days.

To calculate the survival rate of general population cohorts that were matched for age and gender with patient groups, data were used from the database of the Dutch Central Bureau for Statistics (CBS). We considered the survival of the matched population cohort the expected survival of the patient group.

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2.1. Statistical analyses

Discrete variables were compared with the χ^2-test and are presented as numbers and percentages. Continuous variables were compared with the Student *t*-test and analysis of variance (ANOVA). Univariate and multivariate logistic and Cox proportional hazard regression analyses were performed to investigate the impact of perioperative transfusion of blood products on early and late mortality at follow-up. Univariate analyses were used to test for the potentially confounding effect of biomedical and demographic factors on outcome. The cumulative long-term survival was estimated according to the Kaplan–Meier method, comparing differences between groups with the log-rank test. One-, five- and ten-year survival were compared using the time table method and the Wilcoxon test. A $P<0.05$ was used for all tests to indicate statistical significance. All statistical analyses were performed using SPPS version 15.0 (SPSS Inc, Chicago, IL).

3. Results

During a ten-year period (January 1998 until December 2007) 10,626 patients underwent CABG. After excluding patients who were lost to follow-up ($n=122$) and patients who received >10 units of RBC ($n=80$), 10,425 patients were analyzed. The total number of transfused units of RBC was 10,006; the total number of transfused units of fresh frozen plasma (FFP) was 2095; and the total number of transfused units of platelets was 375. The minimum follow-up period for surviving patients was 60 days. Mean follow-up was 1691±1058 days [range: 0 (operative death)–3708 days]. Median was 1629 days.

Baseline characteristics stratified by the number of received units of RBC are shown in Table 1.

Patients in group 1 were more often younger males, had less often chronic obstructive pulmonary disease (COPD) and peripheral vascular disease (PVD), had a better left ventricular function [ejection fraction (EF) >35%], renal function and a higher preoperative hemoglobin level and a shorter duration of ECC (ECC-time). Emergency operations and previous cardiac surgery were seen more frequently in groups 3 and 4. Patients receiving more RBC received also more FFP and platelets.

The incidence of postoperative complications stratified by the number of received units of RBC is shown in Table 2.

Univariate logistic regression analyses revealed the numbers of units of RBC, FFP and platelets as continuous variables as risk factors for early mortality (Table 3).

All risk factors that were identified with univariate logistic regression analyses were entered into a multivariate logistic regression model. The number of units of RBC as a continuous variable was an independent risk factor for early mortality.

Results of Cox regression analyses regarding risk factors of late mortality are shown in Table 4. Univariate analyses revealed the numbers of units of transfused RBC, FFP and platelets as risk factors for late mortality.

All risk factors that were identified with univariate analyses were entered into the multivariate Cox regression model. The number of units of transfused RBC, FFP and platelets were not identified as predictors of late mortality.

Table 2
Postoperative complications stratified by received units of red blood cells

Complication	0 RBC $n=6828$	1–2 RBC $n=2371$	3–5 RBC $n=900$	6–10 RBC $n=326$	*P*-value
Renal failure (need for dialysis)	5 (0.1)	18 (0.7)	16 (1.8)	15 (4.5)	<0.0001
CVA	37 (0.5)	24 (1.0)	15 (1.7)	8 (2.4)	<0.0001
Mediastinitis	41 (0.6)	30 (1.2)	10 (1.1)	7 (2.1)	<0.0001
IABP	43 (0.6)	46 (1.9)	70 (7.8)	55 (16.9)	<0.0001
Re-exploration	97 (1.4)	105 (4.4)	159 (17.7)	166 (50.9)	<0.0001
Periop MI	104 (1.5)	89 (3.8)	66 (7.3)	39 (12.0)	<0.0001

Data are expressed as number (percentage). CVA, cerebrovascular accident; IABP, intra-aortic balloon pump support; Periop MI, perioperative myocardial infarction; RBC, red blood cells.

Table 1
Baseline characteristics stratified by received units of red blood cells

	0 RBC $n=6828$	1–2 RBC $n=2371$	3–5 RBC $n=900$	6–10 RBC $n=326$	*P*-value
Age	63.2±9.4	67.1±9.2	67.7±9.5	67.4±9.3	<0.0001
Male	5934 (86.9)	1387 (58.5)	485 (53.9)	219 (67.2)	<0.0001
Diabetes	1370 (20.1)	554 (23.4)	207 (23.0)	65 (19.9)	0.003
Hypertension	2799 (41.0)	1016 (42.9)	394 (43.8)	142 (43.6)	0.191
COPD	830 (12.2)	291 (12.3)	137 (15.2)	51 (15.6)	0.020
PVD	723 (10.6)	324 (13.7)	111 (12.3)	51 (15.6)	<0.0001
EF<35%	188 (2.8)	97 (4.2)	43 (5.0)	20 (6.8)	<0.0001
CrCl ml·min^{-1}	79.2±25.5	63.4±22.4	60.2±24.1	59.5±25.4	<0.0001
Preoperative Hb g·dl^{-1}	14.3±1.1	13.2±1.3	12.8±1.5	13.0±1.7	<0.0001
Emergency	136 (2.0)	104 (4.4)	100 (11.1)	77 (23.6)	<0.0001
Off-pump	774 (11.3)	110 (4.6)	33 (3.7)	11 (3.4)	<0.0001
Duration of ECC	54.1±33.8	61.9±30.1	66.2±33.9	74.0±43.1	<0.0001
Redo	279 (4.1)	150 (6.3)	126 (14.0)	64 (19.6)	<0.0001
Number of grafts	3.4±1.1	3.5±1.0	3.3±1.1	3.4±1.1	0.002
Number of FFP	0.03±0.26	0.19±0.68	0.58±1.14	2.47±2.32	<0.0001
Number of platelets	0.01±0.01	0.02±0.02	0.09±0.36	0.45±0.82	<0.0001

Results as number (percentage) or mean±S.D. COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; EF, ejection fraction; Preop CrCl, preoperative creatinine clearance; Hb, hemoglobin level; ECC, extra-corporeal circulation; Redo, previous cardiac surgery; FFP, fresh frozen plasma; RBC, red blood cells.

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Table 3
Predictors of early mortality (≤30 days post-CABG); univariate and multivariate logistic regression analyses

Risk factor	Univariate analyses early mortality		Multivariate analysis early mortality	
	HR (95% CI)	*P*-value	HR	*P*-value
RBC	1.308 (1.267–1.351)	<0.0001	1.214 (1.126–1.308)	<0.0001
FFP	1.397 (1.326–1.471)	<0.0001	0.904 (0.783–1.043)	0.165
Platelets	2.806 (2.368–3.326)	<0.0001	1.136 (0.764–1.688)	0.529
Age[a]	1.082 (1.065–1.099)	<0.0001	1.060 (1.036–1.085)	<0.0001
Male gender	0.77 (0.58–1.02)	0.068		
COPD	1.91 (1.41–2.60)	<0.0001	1.84 (1.27–2.65)	0.001
Diabetes	1.48 (1.12–1.96)	0.005	1.59 (1.14–2.23)	0.006
CrCl ml·min^{-1}[a]	0.971 (0.966–0.976)	<0.0001	0.987 (0.979–0.995)	0.002
EF < 35%	6.02 (4.17–8.68)	<0.0001	4.56 (2.86–7.26)	<0.0001
Preop Hb[a]	0.696 (0.640–0.758)	<0.0001	0.997 (0.894–1.113)	0.962
PVD	1.60 (1.16–2.23)	0.005	1.02 (0.67–1.55)	0.906
Redo	4.26 (3.12–5.84)	<0.0001	1.32 (0.81–2.14)	0.259
Emergency	6.78 (4.94–9.31)	<0.0001	1.20 (0.61–2.38)	0.590
Year of operation	0.947 (0.906–0.989)	0.014	1.006 (0.951–1.063)	0.840
ECC-time[a]	1.011 (1.007–1.014	<0.0001	1.003 (0.999–1.006)	0.098
Periop MI	5.78 (3.97–8.43)	<0.0001	3.87 (2.43–6.18)	<0.0001
Re-exploration	5.78 (4.27–7.83)	<0.0001	2.55 (1.63–3.98)	<0.0001
IABP	14.68 (10.51–20.50)	<0.0001	4.76 (2.81–8.05)	<0.0001
Hypertension	0.94 (0.73–1.21)	0.656		
Off-pump	0.68 (0.41–1.17)	0.144		
No grafts[a]	0.912 (0.817–1.018)	0.302		

[a]Entered as a continuous variable. HR, hazard ratio; RBC, red blood cells; FFP, fresh frozen plasma; COPD, chronic obstructive pulmonary disease; Preop CrCl, preoperative creatinine clearance; EF, ejection fraction; Preop Hb, preoperative hemoglobin level; PVD, peripheral vascular disease; Redo, previous cardiac surgery; ECC, extra-corporeal circulation; Periop MI, perioperative myocardial infarction; IABP, intra-aortic balloon pump support; CABG, coronary artery bypass grafting.

Table 4
Predictors of late mortality >30 days post-CABG; univariate and multivariate Cox regression analyses

Risk factor	Univariate analyses late mortality		Multivariate analysis late mortality	
	HR (95% CI)	*P*-value	HR	*P*-value
RBC	1.162 (1.128–1.196)	<0.0001	1.035 (0.994–1.007)	0.091
FFP	1.149 (1.076–1.227)	<0.0001	1.008 (0.928–1.093)	0.856
Platelets	1.333 (1.125–1.732)	0.032	1.197 (0.932–1.537)	0.159
Age[a]	1.094 (1.085–1.103)	<0.0001	1.064 (1.055–1.073)	<0.0001
Male gender	0.83 (0.72–0.96)	0.013	1.54 (1.33–1.77)	<0.0001
COPD	1.80 (1.54–2.10)	<0.0001	1.70 (1.49–1.95)	<0.0001
Diabetes	1.74 (1.52–2.00)	<0.0001	1.50 (1.32–1.71)	<0.0001
CrCl ml·min^{-1}[a]	0.975 (0.972–0.977)	<0.0001	0.989 (0.986–0.993)	<0.0001
EF < 35%	2.59 (2.03–3.31)	<0.0001	2.51 (2.03–3.09)	<0.0001
Preop Hb[a]	0.612 (0.573–0.655)	<0.0001	0.864 (0.825–0.904)	<0.0001
PVD	2.30 (1.97–2.69)	<0.0001	1.54 (1.34–1.78)	0.0001
Redo	1.54 (1.25–1.90)	<0.0001	1.16 (0.94–1.42)	0.148
Hypertension	1.22 (1.07–1.38)	0.002	1.07 (0.95–1.20)	0.256
Year of operation	0.961 (0.938–0.985)	0.002	0.966 (0.940–0.993)	0.012
No. of grafts[a]	1.084 (1.027–1.144)	0.003	0.991 (0.940–1.043)	0.721
Periop MI	1.81 (1.33–2.47)	<0.0001	1.99 (1.54–2.58)	<0.0001
Re-exploration	1.62 (1.29–2.04)	<0.0001	1.52 (1.19–1.93)	0.001
IABP	1.95 (1.38–2.76)	<0.0001	1.94 (1.46–2.59)	<0.0001
Emergency	1.25 (0.93–1.67)	0.128		
Off-pump	0.76 (0.58–1.00)	0.053		

[a]Entered as a continuous variable. HR, hazard ratio; RBC, red blood cells; FFP, fresh frozen plasma; COPD, chronic obstructive pulmonary disease; Preop CrCl, preoperative creatinine clearance; EF < 35, ejection fraction <35%; Preop Hb, preoperative hemoglobin level; PVD, peripheral vascular disease; Redo, previous cardiac surgery; Periop MI, perioperative myocardial infarction; IABP, intra-aortic balloon pump support; CABG, coronary artery bypass grafting.

In Figs. 1 and 2, the long-term and expected survival of the patients receiving 0 or 1–2 RBC and patients receiving 3–5 or 6–10 RBC is shown. Fig. 3 shows the correlation between the number of transfused RBC units and the predicted mortality.

Log-rank test showed significant differences between all patient groups. One, five and nine years survival rates are shown in Table 5. Patients receiving 0 RBC had a better than expected five and nine years survival. No difference was found between the one, five and nine years survival

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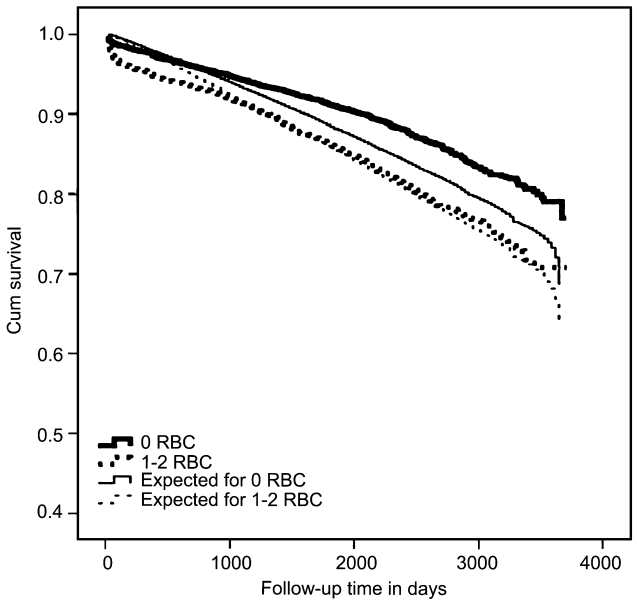

Fig. 1. Kaplan–Meier survival curve stratified by units of transfused red blood cells and the expected survival for patients receiving <3 RBC units.

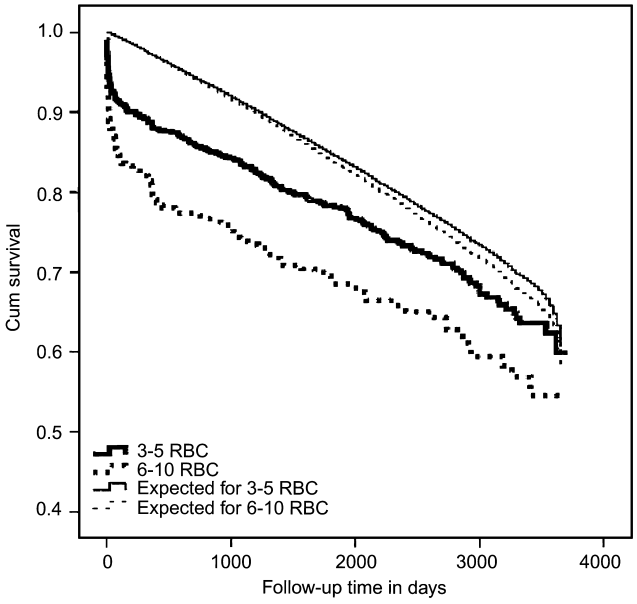

Fig. 2. Kaplan–Meier survival curve stratified by units of transfused red blood cells and the expected survival for patients receiving two RBC units.

rates of patients receiving 1–2 RBC and their expected survival rates, whereas one, five and nine years survival rates of patients receiving >2 RBC were worse than expected.

4. Discussion

This study revealed the number of transfused RBC to be an independent predictor of early but not for late mortality after CABG. Compared to expected survival, we noted that in patients receiving three or more units of RBC survival

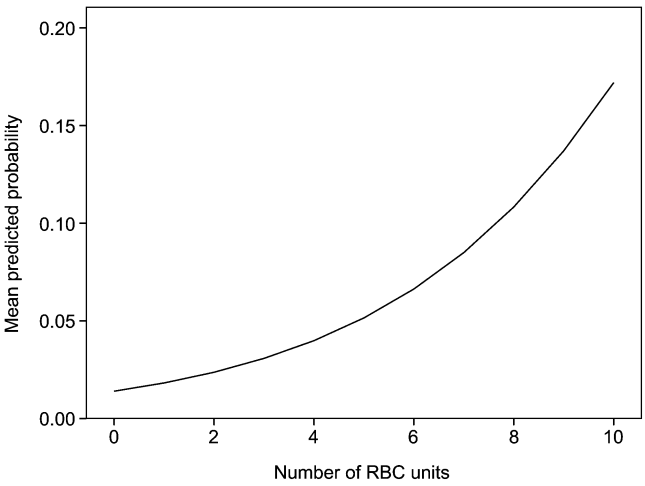

Fig. 3. Correlation between the number of transfused RBC units and the predicted mortality.

Table 5
One, five and ten years observed and expected survival

	1 year	5 years	9 years	*P*-value
0 RBC				<0.0001
Observed	95.9±0.3	89.3±0.5	79.0±1.2	
Expected	95.8±0.1	85.7±0.2	72.7±0.7	
Patients at risk	5659	2565	274	
1–2 RBC				0.363
Observed	93.4±0.5	83.3±0.9	70.8±1.8	
Expected	94.7±0.1	82.5±0.2	67.6±0.5	
Patients at risk	2045	1125	157	
3–5 RBC				<0.0001
Observed	85.8±1.2	75.1±1.8	61.2±2.8	
Expected	94.4±0.1	81.3±0.2	64.5±0.4	
Patients at risk	741	435	63	
6–10 RBC				<0.0001
Observed	77.2±2.4	66.6±2.9	54.7±4.3	
Expected	94.2±0.1	80.3±0.2	62.5±0.4	
Patients at risk	237	131	21	

Nine years because of small numbers at ten years. Results as percentage cumulative survival±S.E. at the time of the interval.

was decreased significantly, whereas receiving no RBC improved patient survival.

Blood products are transfused to increase hemoglobin and thereby improving tissue oxygenation and finally outcome [1, 3, 5–8]. However, several studies suggest that transfusion of blood products may be harmful by increasing the risk of postoperative infection, myocardial or cerebrovascular ischemia, renal failure, poorer functional recovery and death [1–5, 7, 8]. Transfusion of blood products may initiate a second inflammatory response by modification of the patient's systemic response and by directly introducing bioactive substances into the circulation, apart from the primary inflammatory response initiated by cardiopulmonary bypass [2–4, 6, 8, 9]. Our study has shown that patients who received ≥3 RBC units had a higher incidence of postoperative complications. This can explain the higher early mortality in these patients.

According to Koch and colleagues [2], patients who received blood products had a significantly reduced postoperative functional recovery at six months. Kuduvalli et

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al. as well as Murphy et al. described a higher mortality rate in the first 30 days after operation as well as through the first postoperative year in patients who received peri-operative blood transfusions [3, 6]. Engoren et al. found transfusion to be a risk factor for long-term (up to five years) mortality [7]. Koch et al. showed a significantly reduced survival of transfused patients at six months, five and ten years [4]. Our findings of reduced long-term survival in patients receiving peri-operative RBC transfusions are in agreement with these investigations, though in our study the number of RBC transfusions was not identified as an independent predictor of late mortality. Therefore, reduced long-term survival in patients receiving >2 units of RBC might be explained by higher early mortality.

The incidence of re-exploration (in most cases for excessive bleeding) is much higher in patients receiving more RBC. We tried to compensate for this possible confounding effect by entering re-exploration into the multivariate model together with the number of RBC. The threshold of the hemoglobin level for transfusion of RBC in our center is 9 g/dl unless postoperative ischemia is present. The threshold increases to 11 g/dl in case of ischemia. This explains why the incidence of peri-operative myocardial infarction (MI) is higher in patients receiving more RBC. In the present study, peri-operative MI was an independent predictor of early as well as late mortality. After adjustment for excessive bleeding and postoperative ischemia, the number of transfused RBC is still an independent predictor of early mortality.

With regard to other baseline characteristics, the patient groups also appeared to be widely different. Well-known risk factors for early as well as late mortality such as older age, COPD, diabetes, low CrCl, EF<35%, and others were more frequently found in patients receiving more RBC transfusions. These findings are in agreement with the findings of previous reports [2, 4, 5, 7, 8, 10]. When adjusted for these risk factors by multivariate analyses, transfusion of RBC was an independent risk factor for early mortality after CABG. In order to eliminate the confounding effect of exceptional surgical problems we excluded patients who received >10 units of RBC. Such a massive transfusion was mostly caused by massive blood loss or other special circumstances which certainly affect the prognosis.

In our study, the number off-pump coronary artery bypass (OPCAB) operations is relatively small (8.9%). Although OPCAB was not identified as a significant factor for early or late mortality, the number of patients having OPCAB was significantly higher in patients receiving no transfusion than in the other groups. This means that OPCAB can decrease the need for RBC transfusions, which confirms the conclusions of other investigators [11].

We used the Dutch CBS database to calculate the survival of the general population cohorts. This organisation keeps track of mortality rates of the overall Dutch population.

Late survival is highly dependent on age. Because age is significantly different between the patient groups we found it necessary to match for age when comparing long-term survival after CABG to the long-term survival of a matched general population cohort.

Female gender is considered an independent risk factor for early mortality after CABG [12–14]. In this study, we could not confirm this finding. Multivariate analysis, however, designates male gender as risk factor for late mortality. Abramov et al. concluded the same after adjustment for other risk factors [12]. Therefore, we decided to match the general population cohorts for sex.

In patients who did not receive any blood products we observed a better than expected survival. However, these results must be interpreted with care. Before undergoing CABG, patients are screened for severe underlying diseases. If severe underlying disease is present, it is aggressively treated or alternative treatment to CABG is considered, thus, biasing the CABG group. Survival of patients who received 1–2 units of blood products was not significantly different from the expected survival rate.

In patients who received >2 units of blood products a worse than expected survival was noted. When studying the survival curves and life table, it is obvious that after the early postoperative period the curves run parallel. This finding confirms our observation that the number of transfused RBC was not a predictor of late mortality. It might be reassuring for patients to know that if they survive the first postoperative period, their prognosis is not influenced anymore by the blood transfusions they received.

5. Limitations

This is an observational retrospective investigation, in which unknown variables could influence final results. Furthermore, we did not study the effect of duration of RBC storage. This issue has been recently addressed [15]. The strengths of this investigation are the large prospectively collected data set and the follow-up period of ten years.

6. Conclusion

Peri-operative transfusion of RBC is an independent, dose-dependent risk factor for early but not for late mortality after CABG. Compared to expected survival, receiving no RBC improves patient's long-term survival, whereas receiving three or more units of RBC decreases patient survival significantly. This is mainly caused by a higher mortality within the first 30 postoperative days in these patients.

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Interact CardioVasc Thorac Surg 2010;10:37-42; originally published online Oct 8, 2009;
DOI: 10.1510/icvts.2009.214551

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